3. (Amended) A method according to claim 2, wherein the polypeptide has an amino acid sequence that has about 100% sequence identity to a full-length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human or animal.

5. (Amended) A method according to claim 1, wherein the animal is selected from the group consisting of primates, cattle , pigs, poultry, and mice.

10. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope in a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to an antibody or population of antibodies from a naïve human or animal and by binding to an antibody or population of antibodies from the human or same species of animal dosed with the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

11. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one epitope on a therapeutic polypeptide, wherein the epitope binds to an antibody or population of antibodies from a naïve human or animal and binds to an antibody or population of antibodies from the human or same species of animal dosed with the therapeutic polypeptide;

b) determining whether the epitope is an immunodominant epitope by using the antibody or population of antibodies from a naïve human or animal and by using an antibody or population of antibodies from the human or same species of animal dosed with the therapeutic polypeptide; and

c3 c) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

Sub D1 13. (Amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope of a therapeutic polypeptide by using an antibody or population of antibodies from a naive human or animal or population thereof,

b) selecting an immunodominant epitope that is not located in a region of the c4 polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

Sub D 22. (Amended) A method for selecting at least one immunodominant epitope to be modified in a polypeptide, comprising:

a) identifying at least one epitope in the polypeptide recognized by an antibody or population of antibodies from a naïve human or animal or population thereof and recognized by an antibody or population of antibodies from the human or same species of animal or population thereof dosed with the polypeptide, wherein the polypeptide has at least 80% sequence identity to c5 an endogenous polypeptide in the same species of animal; and

b) selecting at least one immunodominant epitope from the identified epitopes by determining whether the identified epitope more frequently elicits an antibody response than other epitopes in the polypeptide.

30. (Amended) A method of modifying a nucleic acid encoding a modified polypeptide c6 comprising:

a) identifying at least one immunodominant epitope in a polypeptide by using an antibody or population of antibodies obtained from a naive human or animal or population thereof;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

31. (Amended) A host cell transformed with the modified isolated nucleic acid of claim 30.

Please add and consider new claims 35-51:

35. (New) A method of modifying a polypeptide, comprising:

a) identifying at least one immunodominant epitope in a polypeptide using an antibody or population of antibodies obtained from a naïve human or population thereof; and

b) modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

36. (New) A method according to claim 35, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 80% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

37. (New) A method according to claim 35, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 85% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

38. (New) A method according to claim 35, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 90% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

39. (New) A method according to claim 35, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 95% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

40. (New) A method according to claim 35, wherein the polypeptide is an isolated polypeptide that has an amino acid sequence that has about 100% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

41. (New) The method according to claim 35, wherein the polypeptide is selected from the group consisting of human thrombopoietin, growth hormones, cytokines, receptors, and humanized antibodies.

42. (New) A method according to claim 35, wherein the modification is a deletion of at least one immunodominant epitope.

43. (New) A method according to claim 35, wherein the modification is a modification of at least one amino acid in the immunodominant epitope by N-glycosylation or pegylation.

44. (New) A method according to claim 35, wherein the modification is a mutation of one or more amino acids in at least one immunodominant epitope.

45. (New) A method according to claim 35, wherein the polypeptide is produced in a non human source.

46. (New) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope on a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to antibody or population of antibodies from a naïve human or population thereof and by binding to an antibody or population of antibodies from a human or population thereof dosed with the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

47. (New) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one epitope on a therapeutic polypeptide, wherein the epitope binds to an antibody or population of antibodies from a naïve human and binds to an antibody or population of antibodies from a human dosed with the therapeutic polypeptide;

b) determining whether the epitope is an immunodominant epitope by using the antibody or population of antibodies from a naïve human and by using an antibody or population of antibodies from a human dosed with the therapeutic polypeptide; and

c) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

48. (New) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope on a therapeutic polypeptide by using an antibody or population of antibodies obtained from a naive human or population thereof, wherein the antibody does not substantially inhibit a therapeutic activity of the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

49. (New) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope of a therapeutic polypeptide by using an antibody or population of antibodies from a naive human or population thereof,

b) selecting the immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

50. (New) A method of modifying a nucleic acid encoding a modified polypeptide comprising:

a) identifying at least one immunodominant epitope on a polypeptide by using an antibody or population of antibodies obtained from a naive human or population thereof;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

51. (New) A host cell transformed with the modified nucleic acid of claim 50.